UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,540	04/15/2005	Stanka Perc	4061-27PUS	1415

27799 7590 08/17/2010

COHEN, PONTANI, LIEBERMAN & PAVANE LLP
551 FIFTH AVENUE
SUITE 1210
NEW YORK, NY 10176

EXAMINER	
JEAN-LOUIS, SAMIRA JM	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
08/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/531,540
Filing Date: April 15, 2005
Appellant(s): PERC ET AL.

Kent H. Cheng
For Appellant

EXAMINER'S ANSWER

This is in response to the Appeal Brief filed on 06/15/10.

The appeal brief is filed in the new format under the revised BPAI final rule before the effective date of the BPAI final rule. The Office published the BPAI final rule to amend the rules governing practice before the BPAI in *ex parte* patent appeals. *See Rules of Practice Before the Board of Patent Appeals and Interferences in Ex Parte Appeals; Final Rule, 73 FR 32938 (June 10, 2008), 1332 Off. Gaz. Pat. Office 47 (July 1, 2008)*. However, the effective date for the BPAI final rule has been delayed. *See Rules of Practice Before the Board of Patent Appeals and Interferences in Ex Parte Appeals; Delay of Effective and Applicability Dates, 73 FR 74972 (December 10, 2008)*. In the notice published on November 20, 2008, the Office indicated that the Office will not hold an appeal brief as non-compliant solely for following the new format even though it is filed before the effective date. *See Clarification of the Effective Date Provision in the Final Rule for Ex parte Appeals, 73 FR 70282 (November20, 2008)*. Since the appeal brief is otherwise acceptable, the Office has accepted the appeal brief filed by appellant.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 34-51 are rejected and are on appeal.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal:

EP 0 830 858	MORRIS	3-1998
3,926,817	NAKAJIMA	12-1975
5,229,382	CHAKRABARTI	7-1993

Pharmaceutics: Science of Dosage Form Design, Tablets, Chapt. 18, pgs. 304-321 RUBENSTEIN 1988

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 34-51 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Morris et al. (EP 0 830 858 A1, previously cited) as evidenced by Nakajima et al. (U.S. 3,926,817, previously cited).

Morris et al. teach an oral formulation where the active ingredient olanzapine is subcoated and mixed with acceptable excipients (instant claim 34, see abstract and pg. 2, lines 49). The anhydrous form of olanzapine (see pg. 2, lines 54-55) was found to overcome the undesirable discoloration problems of the prior art and found to be stable due to the subcoating of the active ingredient (see pg. 2, lines 35-37 and line 50). The formulation is preferably in an uncoated tablet form (instant claim 32; pg. 8, example 3). Morris et al. further teach that the oral formulation can contain diluents such as lactose, binders such as crospovidone and microcrystalline cellulose, disintegrants such as crospovidone, and lubricants and glidants such as magnesium stearate (instant claims 42-45). Morris et al. further teach that the subcoated form II of olanzapine was used

(instant claims 48; see pg. 7, Preparation 2, Form II, lines 15-23) and mixed with 232.12 mg lactose (i.e. 71.4% of b component or oligosaccharide), 13 mg (i.e. 4%) hydroxypropyl cellulose and 40 mg (i.e. 12.3% binder/disintegrant) microcrystalline cellulose (i.e. a total of 16.3% polysaccharide or component (c) or binders), 16.25 mg of crospovidone (i.e. 5% binder) and 1.63 mg of magnesium stearate (i.e. 0.5% lubricant and glidant) (see instant claims 36-41; see pg. 8, example 3). Importantly, Morris et al. teach that the coated olanzapine is blended (i.e. homogeneously mixed) along with the aforementioned excipients and subsequently compressed with the appropriate tooling on tablet compression equipment (See pg. 8, lines 35-39). Morris et al. do not teach the inclusion of solvent during compression so this meets the limitation of claim 35 of the absence of solvents.

Morris et al. however do not teach the use of an uncoated olanzapine in the oral formulation. Similarly, Morris et al. do not specifically teach a cellulose content of 20-30 weight %, 8-12 weight % of crospovidone, or magnesium stearate in an amount of 0.2-0.4 weight %.

While Morris et al. teach the use of coated olanzapine in the blended mixture, Morris et al. also teach that uncoated olanzapine stored in polyethylene bottles do not show discoloration until exposed to air thus suggesting that non-coated olanzapine can be envisioned in oral formulations. Moreover, Morris et al. further teach that uncoated tablets stored at ambient conditions in amber, high density polyethylene bottles do not

show signs of discoloration after 24 months unless the tablets are exposed to open air then discoloration occurs within 5 days (see pg. 4, lines 45-48). Thus, the Examiner contends that it would be within the skilled artisan to formulate the tablets as uncoated tablets if the intended use is for rapid usage of the formulation before the discoloration period and/or for rapid dissolution.

While the exact percentage of the ingredients are not disclosed by Morris, it is generally noted that differences in concentration do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or dosage is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Given that applicant did not point out the criticality of specific percentages of the invention, it is concluded that the normal desire of scientists or artisans to improve upon what is already generally known would provide the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.

Nakajima et al., on the other hand, have been provided to demonstrate that magnesium stearate is known in the art to be a glidant as well (see col. 8, claim 7).

With regard to Claim 50, the Examiner contends that the ingredients taught by Morris would necessarily form a matrix due to the nature and combination of the excipients. If however, applicant believes that such matrix is not formed, it is incumbent

upon applicant to demonstrate through comparative results that such matrix is not formed as a result of the combination of ingredients taught by Morris. As for claim 51, since the Examiner suggests the use of uncoated tablets and Morris teaches a blended mixture which results in an uncoated tablet, the examiner again contends that the tablet does not form a layered structure.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the uncoated olanzapine in the composition of Morris if the desire is for rapid usage before the discoloration time period ensues. Thus, in view of the teachings of Morris et al., one of ordinary skill would have been motivated to utilize uncoated olanzapine in the oral formulation of Morris et al. with the reasonable expectation of providing an oral formulation of olanzapine that rapidly disintegrate and available for fast usage.

Claims 34-51 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Chakrabarti et al. (U.S. 5,229,382, previously cited) in view of Rubinstein et al. (Pharmaceutics: The Science of Dosage Form Design, 1988, Tablets, Chapter 18, pgs. 304-321, previously cited).

Chakrabarti et al. teach the use of olanzapine of formula I in the treatment of disorders of the central nervous system and that the compound has antagonistic properties against the D-1 and D-2 dopamine receptors (see abstract and see col. 2,

lines 38-51). Chakrabarti et al. further teach a pharmaceutical composition comprising as active ingredient a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier (see col. 8, lines 16-20). In making the compositions of the invention conventional techniques for the preparation of pharmaceutical compositions may be used wherein the formulation is made in the form of a tablet (see col. 8, lines 20-22 and lines 40-41). Particularly, Chakrabarti et al. teach the active ingredient of formula I is mixed with a carrier which can be a diluent or excipient (see col. 8, lines 22-29). Suitable carriers include lactose, methyl cellulose, starches, talc, and magnesium stearate (see col. 8, lines 26-35). Chakrabarti et al. additionally exemplify the uncoated olanzapine tablet formulation without any solvent in example 4 where the tablet is made by mixing appropriate diluents such as starches at 68%, lubricants and glidants such as magnesium stearate at 0.3%, disintegrants such as microcrystalline cellulose at 25%, and binders such as povidone at 5.0%, and wherein the tablet is then compressed (instant claims 35, 39-41, 44-45, and 48-49; see col. 11, lines 26-39).

Chakrabarti et al., however, do not teach the use of a monosaccharide as the diluent or the use of 70-80% lactose as the diluent in the oral formulation. Similarly, Chakrabarti et al. do not specifically teach a 3-10 weight % of a binder, 8-12 weight % of povidone, or 3-10 weight % of a disintegrant in the formulation.

Rubinstein et al. teach that a tablet just does not contain the active ingredient (i.e. olanzapine) but also includes other substances known as excipients which have specific functions (see pg. 309, right col., paragraph 2). Particularly, Rubinstein et al. teach the monosaccharide, lactose, as the principal diluent used in the art for bulking the tablet (see pg. 309, right col., paragraph 3). Additionally, Rubinstein et al. teach starches as well-known binding agents and diluents for bulking and as adhesives (see pg. 310, right col., paragraphs 3 and last paragraph; and left col., paragraph 1). Additionally, Rubinstein teaches the use of glidants in tablets to improve flow properties (see pg. 311, left col., last paragraph). Rubinstein et al. particularly teach that the most commonly used and effective glidant is silica at a concentration of 0.1-0.5 % (see pg. 311, left col., last paragraph).

While Chakrabarti does not specifically teach the exact percentages of the ingredients, it is well within the purview of the skill of the artisan at the time of the invention to adjust the concentration and percentage of the ingredients in the composition during the course of routine experimentation so as to obtain the desirable type of product.

While the exact percentage of the ingredients are not disclosed by Chakrabarti, it is generally noted that differences in concentration do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. “[W]here the general conditions of a claim are disclosed in the

prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Given that applicant did not point out the criticality of specific percentages of the invention, it is concluded that the normal desire of scientists or artisans to improve upon what is already generally known would provide the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.

With regard to Claim 50, the Examiner contends that the ingredients taught by Chakrabarti would necessarily form a matrix due to the nature and combination of the excipients. If however, applicant that such matrix is not formed, it is incumbent upon applicant to demonstrate through comparative results that such matrix is not formed as a result of the combination of ingredients taught by Chakrabarti. As for claim 51, since Chakrabarti does not teach coated olanzapine and Chakrabarti teaches a blended mixture which results in an uncoated tablet, the examiner again contends that the tablet does not form a layered structure.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the uncoated olanzapine in the composition of Chakrabarti along with the carriers taught by Chakrabarti in combination since Rubenstein teaches these carriers as well-known excipients in tablet formulations. Thus, in view of the teachings of Chakrabarti et al. and Rubenstein et al., one of ordinary skill would have been motivated to utilize uncoated olanzapine along with carriers taught by Chakrabarti

in combination in the oral formulation with the reasonable expectation of providing an oral formulation of olanzapine that is effective in the treatment of central nervous system disorders.

(10) Response to Argument

A. Rejection over Morris and Nakajima.

(1) Appellant submits that Morris does not disclose a formulation comprising uncoated olanzapine. Appellant further submits that the Examiner solely relies on a single sentence at col. 4, lines 47-49 in Morris to argue that a formulation comprising uncoated olanzapine as recited in the claims is obvious. In fact, Appellant states that in light of the statements of Morris one skilled in the art would not have made uncoated olanzapine formulations.

The Examiner however disagrees because the Examiner contends that the disclosure of Morris does in fact teach uncoated olanzapine (see Morris, pg. 4, lines 45-48). While Morris exemplifies a coated olanzapine, the Examiner contends that uncoated olanzapine were also taught by Morris since Morris explicitly teaches that uncoated tablets of olanzapine stored at ambient temperature did not show signs of discoloration thereby suggesting that such formulation is indeed within the purview of the skilled artisan. Additionally, the Examiner respectfully points out to applicant that the claims are directed to a pharmaceutical formulation comprising uncoated olanzapine, a monosaccharide or oligosaccharide, a polysaccharide and optionally; one or more additional excipients. Morris teaches that uncoated olanzapine can be formulated and further teach addition of lactose (i.e. an oligosaccharide or component (b)), microcrystalline cellulose (i.e. a polysaccharide or component (c) or binders),

hydroxypropyl cellulose, crospovidone, and stearate (i.e. excipients) to olanzapine formulations. Consequently, the Examiner maintains that because Morris teaches that uncoated olanzapine is within the purview of the skilled artisan, the Examiner contends that one of ordinary skill in the art would have indeed found it obvious to formulate a composition comprising uncoated olanzapine and further add the aforementioned components to the composition since Morris demonstrated that uncoated olanzapine can indeed be made.

While applicant argues that one skilled in the art would not select an uncoated tablet among other better choices, the Examiner maintains that obviousness does not hinge on whether better choices existed but rather whether such formulation can be reasonably made and be made successfully. Moreover, the Examiner articulated a reasoning with some rational underpinning (i.e. one skilled in the art would have formulated uncoated olanzapine if the desire is to rapidly consume such formulation) to support the legal conclusion of obviousness as to why one skilled in the art would have formulate an uncoated olanzapine formulation. Thus, if the desire is to provide a formulation of olanzapine that is rapidly consumed or consumed within 5 days, then one of ordinary skill in the art would have indeed found it obvious to formulate an uncoated olanzapine formulation.

As for the recitation of a homogenous mixture, applicant's own brief stipulates that such a mixture can be achieved by the direct compression process wherein olanzapine is first mixed with excipients and then subjecting it to direct compression (see Appeal Brief, pg. 6, last paragraph). Morris also teaches such a process where the

olanzapine can be blended (i.e. homogeneously mixed) along with the aforementioned excipients and subsequently compressed with the appropriate tooling on tablet compression equipment. In view of the foregoing, the Examiner maintains that a homogenous mixture of olanzapine is indeed taught by Morris and is obvious as it is well within the purview of the skilled artisan. Because the Examiner has made a *prima facie* case of obviousness, the Examiner contends that it is therefore incumbent upon applicant to demonstrate that an uncoated olanzapine mixed with the aforementioned ingredients does not result in a homogenous mixture.

> (2) Appellant submits that it is not clear whether Morris refers to (1) tablets without coating on the outmost surface of the final tablet product formed from the mixture of excipients and olanzapine, which may be coated or uncoated or (2) tablets that comprise uncoated olanzapine and excipients. Appellant further argues that one skilled in the art would not formulate a composition comprising uncoated olanzapine that may discolor at any time.

The Examiner however disagrees as the Examiner maintains that Morris was referring to uncoated tablets of olanzapine and not tablets without coating on the outmost surface of the final tablet. In fact, Morris particularly points out such distinction on pg. 4, lines 52-53 wherein Morris teaches the use of coated olanzapine to provide a barrier between the olanzapine drug and excipients. As a result, the Examiner maintains that it is clear that Morris referred to the uncoated drug olanzapine and not an uncoated tablet wherein the outermost surface is uncoated. As for appellant's arguments that one skilled in the art would not formulate an uncoated olanzapine composition since such composition can discolor at any time, such arguments are again not found persuasive as Morris explicitly teaches that uncoated olanzapine composition

can be formulated. Regardless if discoloration can occur at any time, this does not prevent one skilled in the art to make and use such formulation. Again the Examiner reminds appellant that while an uncoated olanzapine might be undesirable, this does not preclude one skilled in the art to formulate an uncoated olanzapine composition. Moreover, the fact that Morris stated that such discoloration occurs within five days suggests to one skilled in the art that stability of such tablets can be maintained for about 5 days. Whether such stability lasts for 24 minutes, 24 hours, or 24 months would not preclude one skilled in the art to make such formulation especially if one skilled in the art intended to rapidly consume such composition.

While applicant argues that such formulation for rapid consumption would be subjected to high manufacturing cost, the Examiner maintains that cost of manufacture would not preclude one of ordinary skill in the art to formulate an obvious product taught by the prior art. Moreover, the Examiner contends that a *prima facie* case of obviousness does not hinge on marketing cost or desirability but is rather governed by the teaching or suggestion of the prior art and if there is reasonable expectation of success.

As for Appellant's arguments that applicant has discovered a tablet formulation with good stability and thus has shown unexpected results, such arguments are not found persuasive as the Examiner continues to maintain that the instant invention is neither unexpected nor unobvious in light of the disclosure of Morris. Nowhere in the claims has appellant recited a limitation for stability nor has appellant defined a threshold for what a stable composition is supposed to be. As a result, the Examiner

maintains that because the claims are simply directed to a composition with uncoated olanzapine mixed with various pharmaceutical ingredients, and because Morris teaches that uncoated olanzapine can be formulated as a composition, Morris does indeed render obvious applicant's invention. As for applicant's arguments on the novelty of the instant invention, the Examiner reiterates the fact that U.S. practice differs from that of WIPO and the EPO. Consequently, findings by the EPO and WIPO have no bearings on U.S. Patent laws. Thus, for the foregoing reasons the Examiner maintains that Morris in view of Nakajima does indeed render obvious appellant's invention.

> (3) Appellants submit that the references do not teach or suggest all of the features of the present independent claims or suggest a formulation of the composition prepared by direct compression. Appellant further argues that Morris does not disclose a matrix composition or a tablet form that does not have a layered structure.

The Examiner again disagrees as the Examiner maintains that formulating an uncoated olanzapine by direct compression is within the purview of the skilled artisan in view of the teachings of Morris. The Examiner refers appellant to Morris who teaches that the olanzapine of the invention is blended (i.e. homogeneously mixed) along with the aforementioned excipients and subsequently compressed with the appropriate tooling on tablet compression equipment. Such recitation does indeed indicate to one skilled in the art that the formulation can indeed be made by direct compression. With regard to the matrix formation, the Examiner contends that such matrix formation is a result of the combination of ingredients and thus such matrix will necessarily be formed due to the combination of excipients taught by Morris. Moreover, because a *prima facie*

case of obviousness was established, it is incumbent upon applicant to demonstrate through comparative results that such matrix is not formed as a result of the combination of ingredients taught by Morris as purported by the Examiner. As for claim 51, since the Examiner suggests the use of uncoated tablets and Morris teaches a blended mixture which results in an uncoated tablet, the examiner maintains that the tablet does not form a layered structure.

B. Rejection over Chakrabarti and Rubinstein.

(1) Appellant submits that Chakrabarti does not teach a homogenous mixture since he teaches a formulation prepared by granulation rather than direct compression. Appellant further submits that the Examiner failed to identify which specific conventional techniques a person of ordinary skill in the art would choose from among other conventional techniques to make a homogenous mixture.

The Examiner however disagrees with applicant's arguments. While Chakrabarti teaches granulating tableting methods, Chakrabarti also teaches that conventional techniques can be used in formulating the composition of his invention (see Chakrabarti, col. 8, lines 40-41 and lines 20-22). Consequently, the Examiner maintains that it would have been obvious to one skilled in the art to formulate the tablet composition of Chakrabarti by direct compression depending on the desired tablet. Given that Chakrabarti teaches the use of conventional techniques and such methods are well-known in the art, the Examiner maintains that formulating the composition of Chakrabarti by direct compression is well within the purview of the skilled artisan. Moreover, the secondary reference, Rubinstein, provided to applicant delineated the conventional techniques known in the tableting art and further indicated various

tableting methods that can be used to formulate tablets including direct compression (see Rubinstein, pg. 307-308). As for appellant's arguments that Chakrabarti does not teach absence of solvents, such arguments are again not found persuasive as the Examiner maintains that Chakrabarti in example 4 clearly demonstrated a dry granulating method and thus teach formulation of a tablet without any solvent (see Chakrabarti, col. 11, example 4). Consequently, the Examiner maintains that in light of the disclosure of Chakrabarti and Rubinstein, the instant invention is neither unexpected nor unobvious.

With regard to the matrix formation limitation of claim 50, the Examiner contends that applicant's own disclosure teaches that the matrix is formed by the components in the formulation. Given that Chakrabarti in view of Rubenstein teaches similar ingredients to the instant invention, the Examiner maintains that it would have been obvious to one skilled in the art to conclude that a matrix will form due to the nature of the composition and given that matrix formation occurs as a result of the mixture of the ingredients in the formulation. Consequently, the examiner maintains that Chakrabarti in view of Rubinstein does indeed render obvious applicant's invention.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Conferees:

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616

/Samira Jean-Louis/

Examiner, Art Unit 1627